REMARKS

Claims 1-42 are pending. Claims 9-15 and 20-42 are under examination. Support for the amendment to the specification on page 46 can be found, for example, on page 4, lines 2-4, which indicates that the domain structure of the Nope protein in comparison to Neogenin, DCC, Punc and NCAM is shown. Accordingly, this amendment to the specification does not raise an issue of new matter and entry thereof is respectfully requested.

Rejection Under 35 U.S.C. § 101 and § 112, First Pargraph

The rejections of claims 9-15 and 20-42 under 35 U.S.C. § 101 and under § 112, first paragraph, as allegedly lacking utility are respectfully traversed. Applicant respectfully submits that the claimed nucleic acids have a specific, substantial and credible utility.

The primary principle of the Utility Examination Guidelines published on January 5, 2001, *66 Fed. Reg. 1092* (January 5, 2001), is the requirement that the utility asserted be well-established or specific, substantial and credible, as judged by one of ordinary skill in the art. The Examiner nevertheless is reminded that the Guidelines and the legal analysis govern the internal operations of the USPTO, but do not have the force and effect of law and cannot, therefore, constitute substantive rules creating or altering the rights or obligations of any party. *66 Fed. Reg. 1097* (January 5, 2001).

Applicant respectfully submits that the specification teaches a specific, substantial and credible utility. Analysis of the Nope sequence revealed that the protein encoded by the Nope nucleic acid sequence contains four immunoglobulin domains and five fibronectin-type domains, has structural similarity to DCC, Punc and NCAM, and most closely resembles cell adhesion molecules (page 46, lines 8-17). The specification further teaches the function of these structurally related proteins as axonal guidance receptors (page 49, line 22, to page 50, line 7). The specification also teaches the developmental expression of Nope, including its expression in cells of the nervous system (Example II, pages 46-48, in particular page 47, line 27, to page 48, line 16). Therefore, Applicant respectfully disagrees with the assertion in the Office Action on page 2 that the specification does not disclose the

biological role of the polynucleotide sequence or its significance. The specification clearly provides an explicit teaching of a specific, subtantial and credible utility of the Nope polynucleotide in that it encodes a protein expressed in the nervous system and that functions as an axonal guidance receptor.

Furthermore, the specification teaches that the Nope gene maps to markers on chromosome 15 that are linked to Bardet-Biedl syndrome 4 (page 57, lines 4-9). Therefore, the specification additionally teaches the utility of the claimed Nope encoding nucleic acids as a chromosome marker for this devastating disease associated with mental retardation.

Applicant refers to the MPEP, § 2107.01, as it relates to utility rejections. In particular under the section "Specific Utility" (MPEP page 2100-32), an example of a claim to a polynucleotide that does not satisfy the utility requirement is a polynucleotide with a disclosed use as a "gene probe" or "chromosome marker" "in the absence of a disclosure of a specific DNA target" (emphasis added). In contrast to this example in the MPEP, the claimed Nope encoding nucleic acids map to a specific chromosome location on chromosome 15, and the specification therefore clearly teaches a specific DNA target, which, as discussed above, can function as a chromosome marker associated with Bardet-Biedl syndrome 4.

Furthermore, Applicant refers to the promulgation of the utility guidelines in the Federal Register, *66 Fed. Reg. 1092* (January 5, 2001). Under the section "Responses to Specific Comments," the position of the USPTO on a number of fact patterns relevant to the examination of nucleic acids is set forth. In particular, under Comment 14, it is indicated that "the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has a gene-regulating activity." As discussed above, the hybridization of the claimed Nope encoding nucleic acids on chromosome 15 in a region linked to Bardet-Biedel syndrome 4 clearly satisfies such a specific and substantial utility.

In the Office Action on page 3, it is asserted that it is unclear whether the protein encoded by the claimed nucleic acid would have the same function in axonal guidance as

the proteins described in the specification having sequence similarity. The Office Action refers to Attwood, Science 290:471-473 (2000), as describing the presumptuousness of making functional assignments "merely on the basis of some degree of similarity between sequences." The Office Action additionally refers to Skolnick et al., Trends Biotech. 18:34-39 (2000), as describing that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins.

With regard to the claimed Nope encoding nucleic acids, the specification teaches that the nucleic acid encodes a polypeptide having four immunoglobulin domains and five fibronectin-type domains, both of which are well characterized structural domains (page 46, lines 8-17). In addition, the specification teaches that Nope is related to axonal guidance receptors (page 49, line 22, to page 50, line 3). Furthermore, the specification teaches that Nope is expressed in the nervous system, consistent with its role in axonal guidance. Therefore, in contrast to the comments in Attwood and Skolnick et al. related to making functional assignments "merely on the basis of some degree of similarity between sequences," the claimed nucleic acids encoding Nope are correlated in the specification with well known structural motifs, proteins with known function, and tissue expression consistent with that function.

The Office Action additionally refers to Metzler et al., Nature Structural Biol. 4:527-531 (1997), as describing single amino acid changes that can alter or abolish the interaction of CTLA4 with its ligands CD80 and CD86 and further asserts that using the protein of the invention would be using it as an object of further research (page 3). With regard to Metzler et al. and the assertion that single amino acid changes can drastically alter functions between two proteins, this reference describes mutagenesis of a conserved region in CTLA-4 containing the MYPPPY motif (completely conserved in 11 of 12 sequences shown, with the only amino acid substitution being a conservative Leu for Met substitution in Cowcd28; Figure 2). In contrast to the assertion in the Office Action, Metzler et al. actually corroborates Applicant's position that conserved domains are predictive of analogous function. The fact that mutation of a conserved domain reduces binding activity is consistent with the conservation of the domain being important for ligand binding, and the

conservation of domains as found in homologous proteins is the basis for why homology analysis is one important criteria that can be used to predict the function of a homologous protein.

Moreover, referring to the utility guidelines referenced above, the issue of using sequence homology is addressed under Comment 19. In particular, the guidelines indicate that "when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. '[A] 'rigorous correlation" need not be shown in order to establish a practical utility: 'reasonable correlation is sufficient," referencing *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1896, 1900 (Fed. Cir. 1996). The guidelines further indicate that "[W]hen a class of proteins is defined such that the members share a specific, substantial and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial and credible utility to the assigned protein.

Applicant respectfully maintains that, at least for the reasons described above, the claimed nucleic acids have a specific, substantial and credible utility. Furthermore, the utility guidelines indicate that "Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement." Applicant respectfully submits that, based on the teachings in the specification and what was well known to those skilled in the art, one of ordinary skill in the art would have understood that the claimed Nope encoding nucleic acid molecules have a specific, substantial and credible utility. Accordingly, Applicant respectfully requests that the utility rejection under 35 U.S.C. § 101 and 112 be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 9-11 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement and of claims 9, 10 and 14 under 35 U.S.C. § 112, first paragraph, as

allegedly lacking written description are respectfully traversed. Applicant maintains, for the reasons of record, that the specification provides sufficient description and guidance for the claimed nucleic acids.

With regard to the term "modification," the specification teaches that a modification of a nucleic acid can include one or several nucleotide additions, deletions or substitutions with respect to a reference sequence, including a substantially the same nucleotide sequence that can hybridize under moderately stringent or higher stringency conditions (page 9, lines 16-30). The specification also teaches various stringency conditions (page 24, line 15, to page 25, line 18). Therefore, Applicant respectfully submits that the specification provides sufficient description and guidance to enable the claimed nucleic acid molecules and modifications thereof. Accordingly, Applicant respectfully requests that the enablement and written description rejections be withdrawn.

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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